

## Lung Burden, Pulmonary Function, and Lung Biochemistry in Rats

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TABLE F9  
Respiratory Frequency of Rats<sup>a</sup>

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	57.11 ± 0.86	55.00 ± 1.13	54.00 ± 0.75*
11-Month Interim	55.33 ± 1.11	56.10 ± 0.92	53.50 ± 0.99
18-Month Interim	56.50 ± 1.34	55.40 ± 1.08	54.60 ± 1.13
24-Month Interim	57.67 ± 1.20	56.50 ± 1.80	56.67 ± 1.86
<b>Female</b>			
6-Month Interim	52.10 ± 0.55	54.50 ± 1.19	54.30 ± 0.90
11-Month Interim	53.60 ± 0.73	53.70 ± 1.10	55.20 ± 0.94
18-Month Interim	55.44 ± 1.12	54.56 ± 0.93	55.22 ± 1.41
24-Month Interim	57.67 ± 1.23	54.44 ± 0.93	59.00 ± 0.58

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

<sup>a</sup> Units are presented as b/min; ratio is (dosed group mean/control group mean)×100TABLE F10  
Total Lung Capacity of Rats<sup>a</sup>

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	19.86 ± 0.54	19.48 ± 0.46	19.25 ± 0.39
11-Month Interim	20.06 ± 0.32	18.44 ± 0.39**	17.67 ± 0.45**
18-Month Interim	20.30 ± 0.45	18.87 ± 0.41*	16.34 ± 0.52**
24-Month Interim	20.50 ± 0.83	20.20 ± 0.28	16.47 ± 1.53
<b>Female</b>			
6-Month Interim	14.20 ± 0.25	14.56 ± 0.27	13.80 ± 0.27
11-Month Interim	13.29 ± 0.21	12.91 ± 0.17	12.06 ± 0.26**
18-Month Interim	13.94 ± 0.26	12.68 ± 0.28**	11.43 ± 0.31**
24-Month Interim	14.85 ± 0.31	13.73 ± 0.34*	11.50 ± 1.07**

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

\*\* P=≤.01

<sup>a</sup> Units are presented as mL; ratio is (dosed group mean/control group mean)×100

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**TABLE F11**  
**Total Lung Capacity/Kilogram Body Weight of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	51.63 ± 1.05	51.45 ± 1.03	53.32 ± 0.78
11-Month Interim	47.71 ± 0.99	44.11 ± 0.87*	43.42 ± 0.74**
18-Month Interim	45.92 ± 1.58	42.98 ± 1.15	38.74 ± 1.50**
24-Month Interim	51.05 ± 4.36	48.49 ± 1.40	44.16 ± 1.29
<b>Female</b>			
6-Month Interim	67.73 ± 1.26	67.06 ± 1.65	65.41 ± 1.50
11-Month Interim	55.21 ± 1.91	52.37 ± 1.05	50.24 ± 1.19
18-Month Interim	45.78 ± 1.26	43.40 ± 1.18	43.26 ± 2.42
24-Month Interim	49.03 ± 1.31	48.93 ± 2.49	44.54 ± 0.51

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

\*\* P≤0.01

<sup>a</sup> Units are presented as mL/kg; ratio is (dosed group mean/control group mean)×100

**TABLE F12**  
**Tidal Volume of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	1.83 ± 0.09	1.90 ± 0.08	2.01 ± 0.10
11-Month Interim	1.94 ± 0.06	1.91 ± 0.06	1.93 ± 0.06
18-Month Interim	1.66 ± 0.08	1.63 ± 0.08	1.74 ± 0.08
24-Month Interim	1.50 ± 0.00	1.85 ± 0.16	2.13 ± 0.19*
<b>Female</b>			
6-Month Interim	1.65 ± 0.07	1.53 ± 0.11	1.40 ± 0.07*
11-Month Interim	1.66 ± 0.07	1.68 ± 0.06	1.43 ± 0.09
18-Month Interim	1.54 ± 0.04	1.34 ± 0.06*	1.40 ± 0.03*
24-Month Interim	1.43 ± 0.08	1.39 ± 0.09	1.37 ± 0.15

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

<sup>a</sup> Units are presented as mL; ratio is (dosed group mean/control group mean)×100

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## Lung Burden, Pulmonary Function, and Lung Biochemistry in Rats

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TABLE F13  
Minute Volume of Rats<sup>a</sup>

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	102.5 ± 3.9	104.8 ± 4.2	104.8 ± 3.4
11-Month Interim	104.5 ± 3.4	106.2 ± 2.3	100.5 ± 2.8
18-Month Interim	97.34 ± 2.79	90.83 ± 3.45	95.87 ± 4.61
24-Month Interim	92.53 ± 2.64	107.25 ± 6.34	117.77 ± 11.70
<b>Female</b>			
6-Month Interim	85.43 ± 4.22	83.05 ± 4.44	76.36 ± 3.45
11-Month Interim	87.89 ± 3.95	88.18 ± 3.26	78.78 ± 3.81
18-Month Interim	87.14 ± 2.71	73.54 ± 3.02**	76.83 ± 2.29**
24-Month Interim	83.87 ± 5.04	79.64 ± 5.29	82.07 ± 5.95

\*\* Significantly different (P=0.01) from the control by Dunn's or Shirley's test

<sup>a</sup> Units are presented as mL/min; ratio is (dosed group mean/control group mean)×100TABLE F14  
Minute Volume/Kilogram Body Weight of Rats<sup>a</sup>

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	266.0 ± 7.0	277.7 ± 12.8	285.1 ± 9.5
11-Month Interim	247.9 ± 5.9	254.5 ± 7.2	247.6 ± 8.2
18-Month Interim	219.4 ± 4.6	206.8 ± 8.2	226.8 ± 10.5
24-Month Interim	229.5 ± 12.7	256.9 ± 14.8	319.9 ± 38.1
<b>Female</b>			
6-Month Interim	408.7 ± 23.3	381.7 ± 19.5	362.7 ± 19.2
11-Month Interim	365.0 ± 18.9	359.3 ± 18.1	330.1 ± 20.7
18-Month Interim	286.2 ± 11.0	250.6 ± 7.6	291.6 ± 17.7
24-Month Interim	276.9 ± 17.4	282.5 ± 21.4	328.8 ± 57.7

<sup>a</sup> Units are presented as mL/min/kg; ratio is (dosed group mean/control group mean)×100

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**TABLE F15**  
**Residual Volume of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	2.90 ± 0.21	2.99 ± 0.17	2.64 ± 0.11
11-Month Interim	2.06 ± 0.17	1.63 ± 0.10	1.70 ± 0.16
18-Month Interim	1.96 ± 0.15	1.74 ± 0.13	1.98 ± 0.16
24-Month Interim	3.23 ± 0.48	2.83 ± 0.19	2.20 ± 0.32
<b>Female</b>			
6-Month Interim	2.18 ± 0.14	2.39 ± 0.22	2.47 ± 0.15
11-Month Interim	1.22 ± 0.15	1.25 ± 0.17	1.65 ± 0.14
18-Month Interim	1.28 ± 0.11	1.52 ± 0.13	1.83 ± 0.13**
24-Month Interim	1.68 ± 0.11	1.72 ± 0.23	1.73 ± 0.19

\*\* Significantly different (P≤0.01) from the control by Dunn's or Shirley's test

<sup>a</sup> Units are presented as mL; ratio is (dosed group mean/control group mean)×100

**TABLE F16**  
**Residual Volume/Total Lung Capacity of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	0.146 ± 0.009	0.154 ± 0.009	0.137 ± 0.004
11-Month Interim	0.102 ± 0.008	0.088 ± 0.005	0.096 ± 0.008
18-Month Interim	0.097 ± 0.007	0.092 ± 0.007	0.121 ± 0.010
24-Month Interim	0.157 ± 0.019	0.140 ± 0.010	0.133 ± 0.011
<b>Female</b>			
6-Month Interim	0.153 ± 0.009	0.163 ± 0.013	0.179 ± 0.011
11-Month Interim	0.091 ± 0.010	0.096 ± 0.013	0.137 ± 0.011*
18-Month Interim	0.091 ± 0.007	0.120 ± 0.010*	0.160 ± 0.009**
24-Month Interim	0.113 ± 0.007	0.125 ± 0.016	0.151 ± 0.005

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

\*\* P≤0.01

<sup>a</sup> Units are presented as mL/mL; ratio is (dosed group mean/control group mean)×100

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## Lung Burden, Pulmonary Function, and Lung Biochemistry in Rats

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TABLE F17  
Vital Capacity of Rats<sup>a</sup>

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	16.96 ± 0.49	16.49 ± 0.44	16.61 ± 0.32
11-Month Interim	18.01 ± 0.27	16.82 ± 0.37*	15.97 ± 0.42**
18-Month Interim	18.35 ± 0.45	17.15 ± 0.38	14.36 ± 0.51**
24-Month Interim	17.27 ± 0.48	17.35 ± 0.34	14.27 ± 1.26
<b>Female</b>			
6-Month Interim	12.02 ± 0.22	12.17 ± 0.20	11.33 ± 0.28
11-Month Interim	12.06 ± 0.20	11.68 ± 0.18	10.40 ± 0.25**
18-Month Interim	12.66 ± 0.21	11.14 ± 0.31**	9.61 ± 0.26**
24-Month Interim	13.15 ± 0.27	11.99 ± 0.32*	9.77 ± 0.90**

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

\*\* P≤0.01

<sup>a</sup> Units are presented as mL; ratio is (dosed group mean/control group mean)×100TABLE F18  
Vital Capacity/Total Lung Capacity of Rats<sup>a</sup>

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	0.854 ± 0.009	0.846 ± 0.009	0.863 ± 0.004
11-Month Interim	0.898 ± 0.008	0.912 ± 0.005	0.904 ± 0.008
18-Month Interim	0.904 ± 0.007	0.909 ± 0.006	0.878 ± 0.010
24-Month Interim	0.843 ± 0.19	0.859 ± 0.010	0.867 ± 0.011
<b>Female</b>			
6-Month Interim	0.847 ± 0.009	0.837 ± 0.013	0.821 ± 0.011
11-Month Interim	0.908 ± 0.010	0.905 ± 0.012	0.862 ± 0.010*
18-Month Interim	0.908 ± 0.007	0.879 ± 0.010*	0.841 ± 0.009**
24-Month Interim	0.886 ± 0.007	0.874 ± 0.016	0.849 ± 0.005

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

\*\* P≤0.01

<sup>a</sup> Units are presented as mL/mL; ratio is (dosed group mean/control group mean)×100

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**TABLE F19**  
**Forced Vital Capacity of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	17.88 ± 0.40	17.15 ± 0.45	17.38 ± 0.41
11-Month Interim	19.03 ± 0.38	18.07 ± 0.43*	17.25 ± 0.45*
18-Month Interim	19.45 ± 0.45	17.92 ± 0.34*	15.28 ± 0.56**
24-Month Interim	17.27 ± 0.61	17.53 ± 0.46	14.90 ± 1.08
<b>Female</b>			
6-Month Interim	12.53 ± 0.33	12.38 ± 0.26	11.27 ± 0.33*
11-Month Interim	12.86 ± 0.25	12.44 ± 0.26	11.22 ± 0.25**
18-Month Interim	13.39 ± 0.24	11.91 ± 0.28**	10.24 ± 0.27**
24-Month Interim	13.08 ± 0.30	12.33 ± 0.33	10.03 ± 0.93**

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

\*\* P≤0.01

<sup>a</sup> Units are presented as mL; ratio is (dosed group mean/control group mean)×100

**TABLE F20**  
**Forced Vital Capacity/Kilogram Body Weight of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	46.48 ± 0.61	45.32 ± 1.18	47.32 ± 1.25
11-Month Interim	45.26 ± 0.95	43.22 ± 0.95	42.42 ± 0.89
18-Month Interim	44.00 ± 1.56	40.82 ± 1.01	36.23 ± 1.57**
24-Month Interim	42.85 ± 2.67	42.00 ± 0.93	40.18 ± 2.32
<b>Female</b>			
6-Month Interim	59.78 ± 1.75	57.01 ± 1.49	53.37 ± 1.48*
11-Month Interim	53.35 ± 1.68	50.43 ± 1.16	46.69 ± 0.90**
18-Month Interim	43.95 ± 1.18	40.76 ± 1.08	38.75 ± 2.17**
24-Month Interim	43.23 ± 1.51	43.87 ± 2.08	38.85 ± 0.48

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

\*\* P≤0.01

<sup>a</sup> Units are presented as mL/kg; ratio is (dosed group mean/control group mean)×100

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## Lung Burden, Pulmonary Function, and Lung Biochemistry in Rats

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**TABLE F21**  
**Functional Residual Capacity of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	4.48 ± 0.25	4.48 ± 0.22	4.17 ± 0.10
11-Month Interim	3.34 ± 0.24	3.16 ± 0.09	3.19 ± 0.12
18-Month Interim	3.24 ± 0.16	3.07 ± 0.11	3.53 ± 0.14
24-Month Interim	4.53 ± 0.52	3.98 ± 0.24	4.37 ± 0.59
<b>Female</b>			
6-Month Interim	3.51 ± 0.12	3.72 ± 0.16	3.57 ± 0.15
11-Month Interim	2.78 ± 0.12	2.74 ± 0.10	2.87 ± 0.14
18-Month Interim	2.47 ± 0.08	2.82 ± 0.12*	3.17 ± 0.14**
24-Month Interim	3.07 ± 0.13	3.31 ± 0.26	3.27 ± 0.18

\* Significantly different ( $P \leq 0.05$ ) from the control by Dunn's or Shirley's test

\*\*  $P \leq 0.01$

<sup>a</sup> Units are presented as mL; ratio is (dosed group mean/control group mean)×100

**TABLE F22**  
**Functional Residual Capacity/Total Lung Capacity of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	0.226 ± 0.012	0.230 ± 0.009	0.217 ± 0.006
11-Month Interim	0.166 ± 0.011	0.172 ± 0.006	0.181 ± 0.007
18-Month Interim	0.159 ± 0.006	0.163 ± 0.005	0.217 ± 0.008**
24-Month Interim	0.220 ± 0.020	0.197 ± 0.012	0.268 ± 0.042
<b>Female</b>			
6-Month Interim	0.248 ± 0.008	0.255 ± 0.009	0.258 ± 0.008
11-Month Interim	0.209 ± 0.008	0.212 ± 0.006	0.238 ± 0.010*
18-Month Interim	0.177 ± 0.007	0.223 ± 0.010**	0.277 ± 0.010**
24-Month Interim	0.207 ± 0.009	0.240 ± 0.016	0.287 ± 0.021*

\* Significantly different ( $P \leq 0.05$ ) from the control by Dunn's or Shirley's test

\*\*  $P \leq 0.01$

<sup>a</sup> Units are presented as mL/mL; ratio is (dosed group mean/control group mean)×100

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**TABLE F23**  
**Total Pulmonary Resistance of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
18-Month Interim	0.075 ± 0.014	0.096 ± 0.009	0.120 ± 0.009*
24-Month Interim	0.110 ± 0.025	0.087 ± 0.028	0.067 ± 0.020
<b>Female</b>			
18-Month Interim	0.130 ± 0.012	0.131 ± 0.016	0.180 ± 0.010*
24-Month Interim	0.138 ± 0.020	0.131 ± 0.014	0.150 ± 0.035

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

<sup>a</sup> Units are presented as cm H<sub>2</sub>O/mL/second; ratio is (dosed group mean/control group mean)×100

**TABLE F24**  
**Maximum Quasistatic Compliance of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	1.97 ± 0.15	1.84 ± 0.12	2.01 ± 0.13
11-Month Interim	2.32 ± 0.10	1.92 ± 0.12*	1.91 ± 0.09*
18-Month Interim	2.35 ± 0.07	2.09 ± 0.16	1.57 ± 0.07**
24-Month Interim	2.00 ± 0.30	2.01 ± 0.11	1.48 ± 0.20
<b>Female</b>			
6-Month Interim	1.37 ± 0.11	1.47 ± 0.11	1.37 ± 0.08
11-Month Interim	1.273 ± 0.062	1.276 ± 0.033	0.968 ± 0.057**
18-Month Interim	1.704 ± 0.108	1.123 ± 0.050**	0.908 ± 0.068**
24-Month Interim	1.538 ± 0.055	1.263 ± 0.062**	0.883 ± 0.093**

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

\*\* P≤0.01

<sup>a</sup> Units are presented as mL/cm H<sub>2</sub>O; ratio is (dosed group mean/control group mean)×100

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## Lung Burden, Pulmonary Function, and Lung Biochemistry in Rats

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TABLE F25  
Quasistatic Chord Compliance of Rats<sup>a</sup>

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	1.18 ± 0.05	1.16 ± 0.04	1.17 ± 0.03
11-Month Interim	1.34 ± 0.02	1.20 ± 0.04*	1.15 ± 0.04**
18-Month Interim	1.343 ± 0.037	1.205 ± 0.040*	0.982 ± 0.037**
24-Month Interim	1.167 ± 0.104	1.220 ± 0.035	0.890 ± 0.124
<b>Female</b>			
6-Month Interim	0.824 ± 0.030	0.895 ± 0.091	0.802 ± 0.024
11-Month Interim	0.841 ± 0.020	0.809 ± 0.016	0.684 ± 0.025**
18-Month Interim	0.879 ± 0.019	0.749 ± 0.027**	0.607 ± 0.030**
24-Month Interim	0.883 ± 0.035	0.764 ± 0.024*	0.573 ± 0.084**

\* Significantly different ( $P \leq 0.05$ ) from the control by Dunn's or Shirley's test\*\*  $P \leq 0.01$ <sup>a</sup> Units are presented as mL/cm H<sub>2</sub>O; ratio is (dosed group mean/control group mean)×100TABLE F26  
Dynamic Compliance of Rats<sup>a</sup>

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	0.546 ± 0.053	0.575 ± 0.043	0.536 ± 0.058
11-Month Interim	0.748 ± 0.041	0.647 ± 0.048	0.687 ± 0.046
18-Month Interim	0.990 ± 0.080	0.741 ± 0.043*	0.685 ± 0.050**
24-Month Interim	0.930 ± 0.173	0.987 ± 0.130	1.173 ± 0.186
<b>Female</b>			
6-Month Interim	0.399 ± 0.029	0.445 ± 0.032	0.380 ± 0.034
11-Month Interim	0.492 ± 0.024	0.426 ± 0.027*	0.393 ± 0.020**
18-Month Interim	0.618 ± 0.053	0.527 ± 0.027	0.372 ± 0.025**
24-Month Interim	0.650 ± 0.065	0.618 ± 0.045	0.377 ± 0.077*

\* Significantly different ( $P \leq 0.05$ ) from the control by Dunn's or Shirley's test\*\*  $P \leq 0.01$ <sup>a</sup> Units are presented as mL/cm H<sub>2</sub>O; ratio is (dosed group mean/control group mean)×100

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**TABLE F27**  
**Peak Expiratory Flow of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	139.9 ± 1.9	138.7 ± 2.8	132.5 ± 4.0
11-Month Interim	136.6 ± 1.4	133.5 ± 4.5	132.9 ± 2.0
18-Month Interim	132.2 ± 1.2	132.3 ± 0.7	129.5 ± 0.6**
24-Month Interim	126.1 ± 2.7	124.5 ± 1.9	124.0 ± 1.0
<b>Female</b>			
6-Month Interim	120.1 ± 8.7	122.3 ± 6.6	113.5 ± 5.7
11-Month Interim	125.3 ± 4.3	123.9 ± 4.9	123.2 ± 2.1
18-Month Interim	120.6 ± 3.0	113.2 ± 2.3	114.3 ± 2.5
24-Month Interim	117.1 ± 2.5	116.7 ± 3.4	110.1 ± 4.7

\*\* Significantly different (P≤0.01) from the control by Dunn's or Shirley's test

<sup>a</sup> Units are presented as mL/second; ratio is (dosed group mean/control group mean)×100

**TABLE F28**  
**Peak Expiratory Flow/Forced Vital Capacity of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	7.85 ± 0.18	8.12 ± 0.22	7.63 ± 0.16
11-Month Interim	7.21 ± 0.18	7.44 ± 0.33	7.74 ± 0.20
18-Month Interim	6.82 ± 0.15	7.40 ± 0.14*	8.57 ± 0.29**
24-Month Interim	7.31 ± 0.14	7.13 ± 0.21	8.40 ± 0.52
<b>Female</b>			
6-Month Interim	9.56 ± 0.62	9.82 ± 0.35	10.08 ± 0.47
11-Month Interim	9.73 ± 0.22	9.95 ± 0.31	11.01 ± 0.23**
18-Month Interim	9.02 ± 0.20	9.57 ± 0.37	11.21 ± 0.32**
24-Month Interim	8.96 ± 0.22	9.47 ± 0.19	11.16 ± 1.13**

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

\*\* P≤0.01

<sup>a</sup> Units are presented as mL/second/mL; ratio is (dosed group mean/control group mean)×100

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## Lung Burden, Pulmonary Function, and Lung Biochemistry in Rats

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**TABLE F29**  
**Expiratory Flow 10% Forced Vital Capacity of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	28.22 ± 2.04	24.20 ± 1.77	19.60 ± 2.67*
11-Month Interim	26.33 ± 1.82	20.80 ± 1.14*	21.60 ± 1.50
18-Month Interim	19.00 ± 1.87	18.00 ± 1.61	20.70 ± 1.17
24-Month Interim	11.33 ± 1.20	18.67 ± 1.50	18.33 ± 1.76
<b>Female</b>			
6-Month Interim	17.40 ± 2.88	18.10 ± 3.10	16.60 ± 2.68
11-Month Interim	19.20 ± 2.36	19.50 ± 1.97	23.30 ± 2.29
18-Month Interim	19.67 ± 1.62	19.00 ± 1.45	21.78 ± 0.66
24-Month Interim	12.67 ± 1.65	18.44 ± 1.51*	17.00 ± 2.52

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

<sup>a</sup> Units are presented as mL/second; ratio is (dosed group mean/control group mean)×100

**TABLE F30**  
**Expiratory Flow 10% Forced Vital Capacity/Forced Vital Capacity of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	1.58 ± 0.11	1.41 ± 0.09	1.13 ± 0.16*
11-Month Interim	1.39 ± 0.10	1.16 ± 0.08	1.27 ± 0.11
18-Month Interim	0.986 ± 0.106	1.002 ± 0.085	1.372 ± 0.085*
24-Month Interim	0.661 ± 0.085	1.057 ± 0.065*	1.256 ± 0.188*
<b>Female</b>			
6-Month Interim	1.37 ± 0.21	1.43 ± 0.23	1.45 ± 0.22
11-Month Interim	1.47 ± 0.17	1.55 ± 0.14	2.07 ± 0.19**
18-Month Interim	1.47 ± 0.13	1.62 ± 0.15	2.14 ± 0.09**
24-Month Interim	0.959 ± 0.109	1.488 ± 0.102*	1.693 ± 0.170*

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

\*\* P≤0.01

<sup>a</sup> Units are presented as mL/second/mL; ratio is (dosed group mean/control group mean)×100

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**TABLE F31**  
**Expiratory Flow 25% Forced Vital Capacity of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	63.56 ± 3.30	55.00 ± 5.57	44.30 ± 6.59*
11-Month Interim	62.00 ± 2.89	60.40 ± 3.46	59.30 ± 3.36
18-Month Interim	50.50 ± 2.57	54.20 ± 2.45	62.20 ± 2.80**
24-Month Interim	47.00 ± 2.89	51.33 ± 3.97	60.00 ± 3.79
<b>Female</b>			
6-Month Interim	44.30 ± 7.73	41.20 ± 7.14	35.60 ± 5.59
11-Month Interim	50.40 ± 5.68	43.00 ± 5.69	54.60 ± 4.01
18-Month Interim	52.33 ± 4.57	42.56 ± 4.76	49.00 ± 3.67
24-Month Interim	40.67 ± 3.80	49.33 ± 6.17	46.00 ± 12.49

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

\*\* P≤0.01

<sup>a</sup> Units are presented as mL/second; ratio is (dosed group mean/control group mean)×100

**TABLE F32**  
**Expiratory Flow 25% Forced Vital Capacity/Forced Vital Capacity of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	3.56 ± 0.19	3.21 ± 0.31	2.54 ± 0.37
11-Month Interim	3.26 ± 0.14	3.35 ± 0.20	3.47 ± 0.24
18-Month Interim	2.61 ± 0.15	3.03 ± 0.14*	4.14 ± 0.27**
24-Month Interim	2.72 ± 0.07	2.92 ± 0.20	4.06 ± 0.35*
<b>Female</b>			
6-Month Interim	3.50 ± 0.59	3.25 ± 0.53	3.10 ± 0.43
11-Month Interim	3.88 ± 0.42	3.43 ± 0.44	4.88 ± 0.37
18-Month Interim	3.91 ± 0.34	3.60 ± 0.44	4.75 ± 0.27
24-Month Interim	3.10 ± 0.24	3.95 ± 0.44	4.66 ± 1.28

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

\*\* P≤0.01

<sup>a</sup> Units are presented as mL/second/mL; ratio is (dosed group mean/control group mean)×100

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## Lung Burden, Pulmonary Function, and Lung Biochemistry in Rats

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**TABLE F33**  
**Expiratory Flow 50% Forced Vital Capacity of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	111.33 ± 7.11	94.00 ± 7.61	78.70 ± 10.05*
11-Month Interim	111.7 ± 4.4	100.1 ± 7.1	102.1 ± 6.2
18-Month Interim	98.75 ± 6.00	97.10 ± 3.59	107.70 ± 5.25
24-Month Interim	99.33 ± 10.17	92.33 ± 4.47	94.67 ± 9.02
<b>Female</b>			
6-Month Interim	75.30 ± 11.98	73.90 ± 10.54	66.00 ± 8.52
11-Month Interim	85.50 ± 8.87	78.00 ± 10.09	94.10 ± 5.57
18-Month Interim	93.00 ± 8.40	76.11 ± 9.60	87.67 ± 6.91
24-Month Interim	86.50 ± 7.12	85.89 ± 10.40	83.67 ± 23.90

\* Significantly different ( $P \leq 0.05$ ) from the control by Dunn's or Shirley's test

<sup>a</sup> Units are presented as mL/second; ratio is (dosed group mean/control group mean)×100

**TABLE F34**  
**Expiratory Flow 50% Forced Vital Capacity/Forced Vital Capacity of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	6.23 ± 0.39	5.50 ± 0.47	4.49 ± 0.55*
11-Month Interim	5.86 ± 0.18	5.55 ± 0.40	5.95 ± 0.40
18-Month Interim	5.08 ± 0.30	5.43 ± 0.21	7.18 ± 0.50**
24-Month Interim	5.73 ± 0.44	5.30 ± 0.36	6.38 ± 0.62
<b>Female</b>			
6-Month Interim	5.95 ± 0.90	5.85 ± 0.77	5.79 ± 0.67
11-Month Interim	6.58 ± 0.62	6.21 ± 0.77	8.39 ± 0.48*
18-Month Interim	6.92 ± 0.59	6.48 ± 0.90	8.49 ± 0.54
24-Month Interim	6.63 ± 0.55	6.88 ± 0.77	8.50 ± 2.50

\* Significantly different ( $P \leq 0.05$ ) from the control by Dunn's or Shirley's test

\*\*  $P \leq 0.01$

<sup>a</sup> Units are presented as mL/second/mL; ratio is (dosed group mean/control group mean)×100

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TABLE F35  
Mean Midexpiratory Flow of Rats<sup>a</sup>

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	101.90 ± 5.20	89.30 ± 7.34	74.27 ± 9.38*
11-Month Interim	102.52 ± 3.54	94.92 ± 6.02	94.11 ± 4.51
18-Month Interim	93.12 ± 3.99	91.41 ± 2.81	98.44 ± 3.67
24-Month Interim	87.13 ± 6.27	87.78 ± 3.74	90.33 ± 7.07
<b>Female</b>			
6-Month Interim	71.07 ± 12.01	70.72 ± 10.66	60.65 ± 7.99
11-Month Interim	81.38 ± 7.94	73.24 ± 9.19	87.91 ± 5.04
18-Month Interim	85.98 ± 6.80	69.51 ± 7.53	81.79 ± 5.58
24-Month Interim	78.28 ± 5.27	79.94 ± 9.44	75.13 ± 19.66

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

<sup>a</sup> Units are presented as mL/second; ratio is (dosed group mean/control group mean)×100TABLE F36  
Mean Midexpiratory Flow/Forced Vital Capacity of Rats<sup>a</sup>

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	5.71 ± 0.30	5.23 ± 0.44	4.24 ± 0.51
11-Month Interim	5.39 ± 0.16	5.27 ± 0.35	5.49 ± 0.32
18-Month Interim	4.78 ± 0.13	5.11 ± 0.18	6.55 ± 0.39**
24-Month Interim	5.04 ± 0.24	5.03 ± 0.29	6.10 ± 0.56
<b>Female</b>			
6-Month Interim	5.62 ± 0.91	5.59 ± 0.78	5.31 ± 0.62
11-Month Interim	6.27 ± 0.56	5.83 ± 0.70	7.85 ± 0.45*
18-Month Interim	6.41 ± 0.48	5.90 ± 0.72	7.94 ± 0.41
24-Month Interim	5.99 ± 0.39	6.40 ± 0.69	7.65 ± 2.13

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

\*\* P≤0.01

<sup>a</sup> Units are presented as mL/second/mL; ratio is (dosed group mean/control group mean)×100

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## Lung Burden, Pulmonary Function, and Lung Biochemistry in Rats

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TABLE F37  
Carbon Monoxide Diffusing Capacity of Rats<sup>a</sup>

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	0.364 ± 0.014	0.347 ± 0.008	0.336 ± 0.010
11-Month Interim	0.400 ± 0.010	0.373 ± 0.010	0.331 ± 0.020**
18-Month Interim	0.338 ± 0.022	0.301 ± 0.015	0.235 ± 0.009**
24-Month Interim	0.303 ± 0.027	0.288 ± 0.011	0.177 ± 0.035*
<b>Female</b>			
6-Month Interim	0.238 ± 0.012	0.241 ± 0.008	0.213 ± 0.010
11-Month Interim	0.233 ± 0.008	0.231 ± 0.005	0.190 ± 0.003**
18-Month Interim	0.233 ± 0.010	0.207 ± 0.009	0.137 ± 0.011**
24-Month Interim	0.198 ± 0.007	0.183 ± 0.006	0.113 ± 0.017**

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

\*\* P≤0.01

<sup>a</sup> Units are presented as mL/minute/mm Hg; ratio is (dosed group mean/control group mean)×100TABLE F38  
Carbon Monoxide Diffusing Capacity/Lung Volume of Rats<sup>a</sup>

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	0.020 ± 0.001	0.020 ± 0.000	0.019 ± 0.000
11-Month Interim	0.021 ± 0.000	0.021 ± 0.001	0.019 ± 0.001*
18-Month Interim	0.017 ± 0.001	0.025 ± 0.008	0.014 ± 0.001*
24-Month Interim	0.015 ± 0.002	0.015 ± 0.001	0.010 ± 0.002*
<b>Female</b>			
6-Month Interim	0.019 ± 0.001	0.019 ± 0.001	0.017 ± 0.001
11-Month Interim	0.018 ± 0.001	0.019 ± 0.000	0.017 ± 0.000*
18-Month Interim	0.017 ± 0.001	0.016 ± 0.001	0.012 ± 0.001**
24-Month Interim	0.013 ± 0.001	0.013 ± 0.001	0.009 ± 0.001

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

\*\* P≤0.01

<sup>a</sup> Ratio is (dosed group mean/control group mean)×100

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**TABLE F39**  
**Carbon Monoxide Diffusing Capacity/Kilogram Body Weight of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	0.949 ± 0.039	0.917 ± 0.017	0.914 ± 0.026
11-Month Interim	0.951 ± 0.021	0.892 ± 0.021	0.821 ± 0.043**
18-Month Interim	0.759 ± 0.043	0.683 ± 0.029	0.554 ± 0.016**
24-Month Interim	0.749 ± 0.056	0.691 ± 0.025	0.465 ± 0.062*
<b>Female</b>			
6-Month Interim	1.13 ± 0.05	1.11 ± 0.04	1.01 ± 0.04
11-Month Interim	0.968 ± 0.045	0.939 ± 0.033	0.792 ± 0.019**
18-Month Interim	0.766 ± 0.034	0.705 ± 0.028	0.502 ± 0.028**
24-Month Interim	0.656 ± 0.031	0.650 ± 0.027	0.435 ± 0.036*

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

\*\* P≤0.01

<sup>a</sup> Units are presented as mL/minute/mm Hg/kg; ratio is (dosed group mean/control group mean)×100

**TABLE F40**  
**Percent Forced Vital Capacity Expired in 0.1 Second of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	61.11 ± 1.52	59.80 ± 2.15	53.90 ± 2.64
11-Month Interim	58.22 ± 0.98	57.40 ± 2.74	60.30 ± 1.63
18-Month Interim	55.00 ± 0.63	58.30 ± 0.90*	66.50 ± 2.13**
24-Month Interim	58.67 ± 1.20	57.00 ± 1.71	64.00 ± 2.89
<b>Female</b>			
6-Month Interim	62.80 ± 5.17	64.20 ± 3.82	63.40 ± 3.86
11-Month Interim	67.00 ± 2.82	65.20 ± 3.61	75.50 ± 1.78*
18-Month Interim	66.44 ± 2.60	64.56 ± 3.57	75.78 ± 1.56*
24-Month Interim	65.83 ± 2.09	66.78 ± 3.31	73.00 ± 9.17

\* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test

\*\* P≤0.01

<sup>a</sup> Units are presented as percent forced vital capacity; ratio is (dosed group mean/control group mean)×100

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## Lung Burden, Pulmonary Function, and Lung Biochemistry in Rats

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**TABLE F41**  
**Slope III of N<sub>2</sub> Washout of Rats<sup>a</sup>**

	0 mg/m <sup>3</sup>	6 mg/m <sup>3</sup>	18 mg/m <sup>3</sup>
<b>Male</b>			
6-Month Interim	0.400 ± 0.023	0.431 ± 0.037	0.481 ± 0.049
11-Month Interim	0.449 ± 0.019	0.446 ± 0.037	0.437 ± 0.040
18-Month Interim	0.393 ± 0.037	0.361 ± 0.035	0.555 ± 0.041*
24-Month Interim	0.627 ± 0.077	0.438 ± 0.045	0.597 ± 0.083
<b>Female</b>			
6-Month Interim	0.587 ± 0.059	0.528 ± 0.049	0.596 ± 0.042
11-Month Interim	0.704 ± 0.027	0.735 ± 0.029	0.813 ± 0.076
18-Month Interim	0.601 ± 0.053	0.699 ± 0.074	1.008 ± 0.087**
24-Month Interim	0.535 ± 0.040	0.580 ± 0.071	1.520 ± 0.409*

\* Significantly different ( $P \leq 0.05$ ) from the control by Dunn's or Shirley's test

\*\*  $P \leq 0.01$

<sup>a</sup> Units are presented as percent N<sub>2</sub>/mL; ratio is (dosed group mean/control group mean)×100

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